NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2023

Futibatinib for treating cholangiocarcinoma with FGFR2 gene rearrangements

Company/Developer	Taiho Oncology Europe

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28942	NICE TSID: 11874	UKPS ID: 668385

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Futibatinib is currently in clinical development for treating relapsed or refractory advanced cholangiocarcinoma (CCA) with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement.

CCA, also known as bile duct cancer, is a rare disease in which malignant cells are formed in the bile duct. FGFRs are receptor enzymes that are involved in several biological process such as tissue repair. Alterations in FGFRs can lead to the development or progression of cancer. CCA symptoms are usually hard to spot but could include itchy skin, darker urine, pale stool, loss of appetite, chronic fatigue, high temperature and shivering. The causes of CCA remain unknown. However, adults aged 65 and older are reported to have an increased risk of developing the disease. There remains a need for potent FGFR inhibitors that are less susceptible to drug resistance.

Futibatinib is an FGFR inhibitor that is administered orally in patients. It works selectively by targeting FGFR mutations to prevent the growth of cancer cells. If licensed, futibatinib will offer an additional treatment option for patients with CCA harbouring FGFR2 gene rearrangements.

Proposed Indication

Treating relapsed or refractory advanced cholangiocarcinoma (CCA) with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement.[1]

Technology

Description

Futibatinib is a highly selective and irreversible FGFR1—4 inhibitor that binds covalently with a protein in the P-loop of the kinase domain to capture multiple FGFR P-loop conformations.[2] FGFRs are receptor tyrosine kinases with a role in several biological processes, such as regulation of development and tissue repair. Alterations in FGFRs such as amplifications, fusions and mutations can lead to the development or progression of cancer.[3]

Futibatinib is currently in clinical development for treating relapsed or refractory advanced CCA with FGFR2 fusion or rearrangement. In the phase 1/2 clinical trial (NCT02052778), patients received 8-200 milligrams (mg) futibatinib orally three times a week or 4-24mg once daily.[1]

Key Innovation

There remains a need for potent FGFR inhibitors that are less susceptible to drug resistance. Despite showing promising results in tumours harbouring FGFR aberrations, most FGFR inhibitors are reversible adenosine 5′-triphosphate (ATP)-competitive inhibitors which are limited by the development of resistance due to acquired mutations. Futibatinib is a structurally novel, irreversible FGFR inhibitor that has demonstrated potent antiproliferative activity against FGFR mutants, with fewer drug-resistant clones when compared to ATP-competitive inhibitors.[4] If licensed, futibatinib will offer an additional treatment option for patients with CCA harbouring FGFR2 gene rearrangements.

Regulatory & Development Status

Futibatinib does not currently have Marketing Authorisation in the UK for any indication.

Futibatinib is in phase II and III clinical development for the following indications:[5]

- Breast cancer
- Biliary tract neoplasms
- Endometrial carcinoma
- Hepatocellular carcinoma
- Non-small cell lung cancer
- Urothelial carcinoma
- Solid tumours with FGFR aberrations

Futibatinib has the following designation/award:

- a Breakthrough Therapy by the US FDA for treatment of patients with previously treated locally advanced or metastatic CCA harbouring FGFR2 gene fusions in 2021.[6]

Patient Group

Disease Area and Clinical Need

CCA, also known as bile duct cancer, is a rare disease in which malignant cells are formed in the bile duct.[7] Ducts are small tubes that connect the liver, gallbladder, and small intestine. CCA is classified based on its location; an intrahepatic cholangiocarcinoma is a type of cancer formed in the bile ducts inside the liver whereas a type of cancer formed in the bile ducts outside the liver is called an extrahepatic cholangiocarcinoma. Symptoms of CCA are usually hard to spot but could include itchy skin, darker urine, pale stool, loss of appetite, chronic fatigue, high temperature and shivering. Although the cause of CCA is unknown, medical conditions such as abnormal bile ducts and long term swelling in the bowel (ulcerative colitis) are considered risk factors.[8] Adults over the age of 65 also have a higher chance of developing the disease.[8] Locally advanced cancer is when the cancer has grown outside of its original site but has not spread to other parts of the body and is incurable. Metastatic cancer occurs when the cancer has spread to other areas of the body and may or may not be advanced.[9] FGFR alterations are present in 5 – 10% of all human cancers, although this frequency increases to 10 – 30% in intrahepatic CCA.[10]

According to the National Cancer Intelligence Network's (NCIN), the crude incidence rate of CCA in England in 2013 was 3.65 per 100,000, and crude mortality rate was 4.01 per 100,000.[11] For people in England in 2012, diagnosed with biliary tract cancer for all stages, nearly 30 out of 100 (almost 30%) men and 25 out of 100 (25%) women survived their cancer for 1 year or more.[12] For people in England, in 2008, diagnosed with biliary tract cancer for all stages, 5 out of 100 men and women (around 5%) survived their cancer for 5 years or more.[12] In England, 2021-22, there were 10,552 finished consultant episodes (FCE) and 7,749 admissions for intrahepatic bile duct carcinoma (ICD-10 code C22.1) which resulted in 29,588 FCE bed days and 5,358 day cases.[13] In England, 2021-22, there were 1,860 finished consultant episodes (FCE) and 1,381 admissions for extrahepatic bile duct carcinoma (ICD-10 code C24.0) which resulted in 5,508 FCE bed days and 997 day cases.[12]

Recommended Treatment Options

Treatment options for CCA include surgery, chemotherapy, radiotherapy, and targeted cancer drugs. NICE currently recommends pemigatinib for the treatment of relapsed or refractory advanced CCA with FGFR2 fusion or rearrangement.[14]

Other common treatments include:[15]

- gemcitabine and cisplatin
- chemotherapy combination FOLFOX

Clinical Trial Information

Trial	NCT02052778; Phase 1/2 Study of TAS-120 in Patients with Advanced Solid Tumors Harboring FGF/FGFR Aberrations **Phase I/II** – Active, not recruiting **Location(s):** Five EU countries, UK, USA, Canada, and other countries **Primary completion date:** May 2021
Trial Design	Non-randomised, sequential assignment, open label
Population	N=386 (actual); adults ≥18 years old; histologically or cytologically confirmed locally advanced or metastatic cancer with at least one FGF/FGFR aberration

Intervention(s)	Futibatinib oral tablets
Comparator(s)	No comparator
Outcome(s)	Primary outcomes: • Phase 1 (dose escalation): Safety and recommended Phase 2 dose (RPTD) [Time frame: baseline until 30 days after end of study treatment; up to 18 months (estimated)] • Phase 1 (dose expansion): Objective response rate (ORR) [Time frame: baseline to end of study treatment; up to 24 months (estimated)] • Phase 2 - Objective response rate (ORR) [Time frame: baseline to end of study treatment; up to 24 months (estimated)] See trial record for full list of other outcomes.
Results (efficacy)	A total of 43 of 103 patients (42%; 95% confidence interval, 32 to 52) had a response, and the median duration of response was 9.7 months. Responses were consistent across patient subgroups. At a median follow-up of 17.1 months, the median progression-free survival was 9.0 months and overall survival was 21.7 months.[16]
Results (safety)	Common treatment-related grade 3 adverse events were hyperphosphatemia (in 30% of the patients), an increased aspartate aminotransferase level (in 7%), stomatitis (in 6%), and fatigue (in 6%). Treatment-related adverse events led to permanent discontinuation of futibatinib in 2% of the patients. No treatment-related deaths occurred. Quality of life was maintained throughout treatment.[16]

Estimated Cost

Cost of futibatinib was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722). August 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 Standard Contract for Cancer: Teenagers & Young Adults. B17/S/a.

Other Guidance

- European Society of Medical Oncology (ESMO). Biliary tract cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2022.[17]

Additional Information

References

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.